UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,052	08/19/2003	Arthur M. Krieg	C1037.70048US00	4791

23628 7590 08/05/2010

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
08/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,052	KRIEG ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *100-102 and 105-118* is/are pending in the application.

4a) Of the above claim(s) *115-118* is/are withdrawn from consideration.

5)☐ Claim(s) *100-102 and 105-107* is/are allowed.

6)☒ Claim(s) *108-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 4-28-10. Claim 100 is amended. Claims 108-114 are new. Claims 115-118 are withdrawn from consideration. Claims 1-99 and 103-104 are cancelled. Claims 100-102 and 105-118 is pending. Claims 100-102 and 105-114 are under examination.

Election Restriction

2. Newly submitted claims 115-118 are directed to a **species (see pgs. 4 of the Office action mailed on 6/30/06) that was not elected and is hereby withdrawn (see Applicants response to election restriction filed 8/2/2006). Applicants elected SEQ ID NO: 313 in the election restriction filed 8/2/2006.** Therefore because Applicants elected the species aforementioned above and since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 115-118 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Objections/Rejections Withdrawn

3. In view of the Applicant's amendments and remarks the following objections/rejections are withdrawn.

a) The rejection of claims 100-102 and 104-107 under 35 U.S.C. 103(a) as being unpatentable in view of Krieg et al WO/01/22972A2 April 5, 2001 and Samani et al Antisense and Nucleic Acid Drug Development 2001 Vol. 11 pgs. 129-136 is withdrawn in light of applicant's amendment thereto and in light of applicant's arguments.

New Grounds of Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claim 108 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 20 of U.S. Application No. 11/361,313.

Claim 20 of U.S. Application No. 11/361,313 teach an immunostimulatory nucleic acid molecule having at least one cytosine-guanine (CG) dinucleotide and a chimeric backbone, wherein the at least one internal CG dinucleotide has a phosphodiester internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized.

Although the conflicting claims are not identical, they are not patentably distinct. The U.S. Application No. 11/361,313 recites the "an immunostimulatory nucleic acid molecule". The species of the an immunostimulatory nucleic acid molecule anticipate the genus claims of any an immunostimulatory nucleic acid molecule.

Thus, claim 108 encompassing the immunostimulatory nucleic acid molecule in the present application are obvious over claim 20 of U.S. Application No. 11/361,313.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claim 114 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 114 recites the phrase, "optionally" and "preferably". The claim language is confusing because it is unclear how Applicant states optionally and then preferably for the structure of the oligonucleotide. Therefore, the skilled artisan would not be readily apprised of the metes and bounds of the structure of the oligonucleotide nor how to assess such. Therefore it is unclear how to interpret the structure oligonucleotide. Appropriate correction is advised.

b) Claim 114, recites the limitation, "5'T*C_G(N_6C_G N_7)$_{2-3}$T*C_G*T*T3'" set forth in the oligonucleotide of SEQ ID NOs: 311-312, wherein the oligonucleotide has a length of 16-40 nucleotides. The skilled artisan would not be readily apprised of the metes and bounds of the length of the oligonucleotide with the recited limitation of "5'T*C_G(N_6C_G N_7)$_{2-3}$T*C_G*T*T3'" nor how to assess such because the recited limitation "5'T*C_G(N_6C_G N_7)$_{2-3}$T*C_G*T*T3'" is more than 16-40 nucleotides in length. Therefore it is unclear how to interpret the length of the structure of the oligonucleotide. Appropriate correction is advised.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 108-114 under 35 U.S.C. 103(a) as being unpatentable in view of Krieg et al WO/01/22972A2 April 5, 2001 as evidenced by Yamamoto et al, 1994 Microbiol. Immunol. 38: 831-836.

The claimed invention is drawn to an immunostimulatory nucleic acid molecule having at least one cytosine-guanine (CG) dinucleotide and a chimeric backbone, wherein the at least one internal CG dinucleotide has a phosphodiester internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized (claim 108), wherein the immunostimulatory nucleic acid comprises a plurality of internal CG dinucleotides having a phosphodiester internucleotide linkage (claim 109), wherein the immunostimulatory nucleic acid molecule is a B-Class immunostimulatory nucleic acid molecule (claim 110), wherein the immunostimulatory nucleic acid molecule is 4-100 nucleotides long (claim 111), wherein the immunostimulatory nucleic acid molecule is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme (claim 112), wherein the nucleic acid has a backbone comprising deoxyribose or ribose (claim 113); an oligonucleotide comprising: 5'T*C_G(N_6C_G N_7)2_3T*C_G*T*T3' (SEQ ID NOs: 311-312) (claim 114).

Krieg et al teach the sequence 343s (i.e. tcgtcgttttgacgttttgtcgtt), wherein sequence 343s (s = phosphorothioate internucleotide linkages) (see table 4 sequence 343 pg. 45), which correlates to an immunostimulatory nucleic acid molecule having at least one internal cytosine-guanine (CG) dinucleotide, wherein optionally each additional internal YZ dinucleotide stabilized internucleotide linkage. Thus, the sequence 343s (i.e. tcgtcgttttgacgttttgtcgtt), wherein sequence 343s (s = phosphorothioate internucleotide linkages) (see table 4 sequence 343 pg. 45) of Krieg et al would also necessarily teach an immunostimulatory nucleic acid molecule, wherein the internucleotide linkages are

stabilized with a phosphorothioate internucleotide linkage, wherein the immunostimulatory nucleic acid molecule is a B-Class immunostimulatory nucleic acid molecule, wherein said oligonucleotide is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme.

Krieg et al teach a sequence 343s (i.e. tcgtcgttttgacgttttgtcgtt), wherein sequence 343s (s = phosphorothioate internucleotide linkages) (see table 4 sequence 343 pg. 45), wherein sequence 343 correlates to SEQ ID NO: 313 as an oligonucleotide comprising tcgtcgttttgacgttttgtcgtt which is the elected species of the instant application and which correlates to the formula (i.e. 5'T*C_G(N_6C_G N_7)$_{2-3}$T*C_G*T*T3') set forth in SEQ ID NOs: 311-312, wherein N_6 is 1 and N_7 is 5 nucleotides in length, and optionally N6 is one nucleotide, preferably T or A and optionally N7 is preferably TTTTG wherein * refers to the presence of a phosphorothioate internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides.

Krieg et al teach a composition comprising an immunostimulatory nucleic acid consisting essentially of: 5' M_1TCGTCGTTM_2 3', wherein at least one of the Cs is unmethylated, wherein M_1 is a nucleic acid having at least one nucleotide, wherein M_2 is a nucleic acid having between 0 and 50 nucleotides, and wherein the immunostimulatory nucleic acid has less than 100 nucleotides (see Krieg et al claim 102) which correlates to an immunostimulatory nucleic acid, wherein said immunostiumulatory nucleic aid sequence of 4-10 nucleotides in length. Krieg et al teaches that the immunostimulatory nucleic acid may be any size (i.e., length) provided it is at least 4 nucleotides and the immunostimulatory nucleic acids can have a length in the range of between 6 and 100 (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al does not specifically teach an internal CG dinucleotide with a chimeric backbone in an immunostimulatory nucleic acid molecule. Additionally, Krieg et al does not specifically teach an immunostimulatory nucleic acid comprising an internal CG dinucleotide, wherein at least one internal CG has a phosphodiester internculeotide linkage in an immunostimulatory nucleic acid with a chimeric backbone. Thirdly, Krieg et al does not specifically teach an oligonucleotide set forth in SEQ ID NOs: 311-312,

wherein _ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides.

Krieg et al teach stabilized nucleic acids have a modified backbone and it has been demonstrated that modification of the nucleic acid backbone provides enhanced activity when administered in vivo (see pg. 38). Krieg et al teach stabilized structures of the invention can have at least a partial modified backbone and constructs having phosphorothioate linkages provide maximal activity and protect the nucleic acid from degradation by intracellular exo-and endo-nucleases (see pgs 38-40). Krieg et al teach modified nucleic acids include internucleotide phosphodiester modified nucleic acids, and also combinations of phosphodiester and phosphorothioate nucleic acid, methylphosphonate, methylphosphorothioate, phosphorodithioate, p-ethoxy, and combinations thereof (see pg. 38 lines 5-15). Krieg et al teach modified nucleic acids may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization (see abstract, pgs. 27-30). Krieg et al as evidenced by Yamamoto et al teach phosphodiester CpG ODN can be formulated in vehicles will improve cell uptake in order to enhance the immune stimulatory effects (see pgs. 2-5).

Although Krieg et al is silent to teaching an immunostimulatory nucleic acid molecule comprising an internal CG dinucleotide having a phosphodiester internculeotide linkage in an immunostimulatory nucleic acid. Krieg et al teach phosphodiester internculeotide linkage, for the purpose of being formulated in vehicles to improve cell uptake in order to enhance the immune stimulatory effects (see pgs. 27-30).

It would have been prima facie obvious at the time the invention was made to incorporate phosphodiester internculeotide linkage as taught by Krieg et al in the CG dinucleotide and the oligonucleotide set forth in SEQ ID NOs: 311-312, in order to take advantage of using vehicles to improve cell uptake in order to enhance the immune stimulatory effects (as disclosed by Krieg et al see pgs. 27-30).

It would have been equally obvious to at the time the invention was made to incorporate phosphodiester internculeotide linkage in the CG dinucleotide with a chimeric backbone in order to take advantage of modified nucleic acids that show more

stimulatory activity due to enhanced nuclease resistance and increased cellular uptake, increased protein binding (as disclosed by Krieg et al see pgs. 27-30).

One would have reasonable expectation of success because internal CG dinucleotide with a chimeric backbone in an immunostimulatory nucleic acid molecule and internal CG dinucleotide with a phosphodiester internculeotide linkage to improve cellular uptake is well known in the art.

Conclusion

7. Claims 100-102 and 105-107 are free of the art of record.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisors, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina Archie
Examiner
Art Unit 1645

/N. M. Minnifield/
Primary Examiner, Art Unit 1645